REMARKS

Summary of Office Action

Examination of claims 11-13, 15-26, 32, 33, and 47 is reported in the present Office Action. Claims 16-19, 23, and 32 are rejected under 35 U.S.C. § 112, first paragraph. Claims 11-13, 15, 19-21, 24, and 25 are rejected under 35 U.S.C. § 102(b). Claims 11-13, 15, 19-22, 24-26, 32, 33, and 47 are rejected under 35 U.S.C. 103(a). Each of the rejections is addressed below.

Summary of Invention

The invention generally features nucleic acid sequences having 99% identity to tanapox virus nucleic acid sequence, SEQ ID NO:5, which encodes an immunomodulatory polypeptide (SEQ ID NO:4), and cells and vectors containing such sequences.

Objections to the Drawings

Replacement drawings are submitted that conform with 37 C.F.R. § 1.84 or 1.152. The drawings were amended to correct the margins. No new matter has been added.

Rejection under 35 U.S.C. § 112, first paragraph

Written Description

Claims 23 was rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner asserts that applicants have failed to describe a gene therapy vector, because the specification does not define how a gene therapy vector differs from a naturally occurring virus. Claim 23 is now directed to an expression vector that directs expression of a nucleic acid having 99% nucleic acid sequence identity to SEQ ID NO:5 in a mammalian cell. Applicants clearly describe such vectors and distinguish them from a naturally occurring virus. For example, at page 18, line 16, to page 19, line 4, applicants describe vectors that are *genetically engineered* to express a coding sequence in a host cell. Examples of vectors useful for transferring a nucleic acid into a mammalian cell are described at page 28. In particular, at page 28, lines 6-20, applicants disclose that retroviral vectors, adenoviral vectors, and adeno-associated viral vectors may be used to transfer a Yatapoxviral gene into a cell, such as a mammalian tumor cell; and at page 29, lines 8-16, applicants teach that a vector may express a Yatapoxviral gene under the control of a suitable promoter. Specifically, applicants state:

> . . . *Yatapoxvirus* or *swinepox* virus (C1L) gp38 cDNA expression is directed from any suitable promoter (*e.g.*, the human cytomegalovirus, simian virus 40, or metallothionein promoters), and its production is regulated by any desired mammalian regulatory element. For example, if desired, enhancers known to direct preferential gene expression in endothelial or epithelial cells may be used to direct *Yatapoxvirus* or *swinepox* virus (C1L) gp38 protein expression. Such enhancers include, without limitation, the lung specific promotors (*e.g.* surfactant),

and gut specific regulatory sequences.

In sum, applicants plainly describe vectors useful for transferring a nucleic acid, such as a nucleic acid having 99% identity to SEQ ID NO:5 or a nucleic acid encoding a polypeptide having 99% identify to SEQ ID NO:4 into a mammalian cell, and distinguish such vectors from naturally-occurring viruses. Thus, the written description rejection should be withdrawn.

Enablement

Claims 16-19 and 23 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Applicants note that claim 19 has now been cancelled.

Claim 23

Claims 23 was rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Examiner based this rejection on the following grounds: (i) that in the absence of *in vivo* clinical data use of a gene therapy vector is unpredictable; (ii) applicants have failed to provide a working example of a gene therapy vector; and (iii) that undue experimentation would be required to practice the methods of the invention. As detailed above, claim 23 is now directed to a vector that expresses SEQ ID NO:5 in a mammalian cell. Applicants have clearly enabled such vectors. Methods for producing and using such a vector are described at page 18, lines 16, to page 19, line 4, and at pages 28 to 30. Specifically, at page 16, lines 16-22, applicants teach that such a vector is a plasmid or virus containing a polypeptide coding sequence operably linked to a promoter,

which may be transferred into a host cell, such that the polypeptide is expressed in the host cell. At page 28, applicants teach methods of gene transfer, including transfection with calcium phosphate, DEAE dextran, electorporation, protoplast fusion, and liposomes. Alternatively, at page 29, lines 1-7, applicants teach that such vectors may be administered via microinjection to the site of a malignancy under surgical conditions or may be applied to a tissue in the vicinity of a malignancy, inflammation, or cytotoxic damage, or may be administered to a blood vessel supplying these areas. Provided with such guidance, the skilled artisan could make and use an expression vector containing a nucleic acid sequence having 99% identity to SEQ ID NO:5 for expression in a mammalian cell. Thus, the enablement rejection should be withdrawn.

Claims 16-19 and 32

Claims 16-19 and 32, which are now directed to nucleic acids and probes having at last 99% nucleic acid sequence identity to SEQ ID NO:5 or encoding a polypeptide having 99% identify to SEQ ID NO:4, were rejected as lacking enablement. Specifically, the Examiner asserts (i) that it would require undue experimentation to produce and test the function of a nucleic acid sequence having 50%-99% sequence identity to SEQ ID NO:5; and (ii) that it would be unpredictable whether nucleic acids having 50%-99% identity to SEQ ID NO:5 would have the same function as the reference sequence.

The Federal Circuit has made clear the level of teaching needed to enable a claim with respect to the prior art, and has stated that a patent need not reiterate techniques

known to skilled workers in a particular area of technology. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed Cir. 1988). In view of this standard, the skilled artisan provided with applicants' specification, which includes the nucleic acid sequence of SEQ ID NO:5 could recognize immunomodulatory nucleic acids falling within the scope of the present claims and would understand that obtaining such nucleic acids would not constitute undue experimentation.

Contrary to the Examiner's assertions, applicants provide detailed methods that allow the skilled artisan to predictably practice the methods of the invention. Methods for identifying Yatapox-related gp38 genes are described at page 47, lines 1-26, under the heading "Cloning Additional Yatapoxvirus-Related gp38 Genes." Applicants teach that additional immunomodulatory nucleic acids can be identified using standard techniques, including the polymerase chain reaction, DNA hybridization, and degenerate primers. Methods for expressing the identified nucleic acids are provided at pages 50-51, under the heading "Construction and Transfection of Protein Expression Vectors," where applicants describe subcloning the isolated nucleic acid into an appropriate vector, such as pcDNA-I/Amp or MoLTR-SV40 I/PA; methods for transfecting the vector into an appropriate cell line, such as COS or J558L cells; and methods for optimizing protein expression.

Methods for evaluating the immunomodulatory activity of the polypeptide expressed by the identified nucleic acid are described at pages 51-52, under the heading

Chemotaxis Assays. Applicants teach that isolated the effects of the expressed protein is evaluated in a Chemotaxis assay using eosinophils or macrophages. Proteins that inhibit eosinophil or macrophage migration are identified as having immunosuppressive properties. Each of the methods described for isolating and characterizing an immunomodulatory gene sequence involves standard techniques routinely used in the art of molecular biology at the time applicants filed their application. None constitutes a step requiring undue experimentation.

Optionally, the efficacy of proteins identified in *in vitro* assays may be tested *in vivo*, using the assays described by Applicants at pages 36-42, under the heading "Animal Models." Applicants teach that identified immunomodulators may be characterized in an animal model of acute inflammation (page 36, lines 16-24), in rat, mouse, or rabbit models of arthritis (page 36, line 25, to page 38, line 4), in rat, rabbit, or monkey models of transplant rejection (page 38, line 6, to page 39, line 17); in a rat model of reperfusion injury; in a rat or mouse model of asthma (page 40, lines 5-20); in mouse or rat models of inflammatory bowel disease (page 40, lines 21, to page 41, line 11); and in a mammalian model of uveitis.

In sum, applicants have plainly described methods for identifying and characterizing nucleic acids having at least 99% nucleic acid sequence identity to SEQ ID NO:5 or a nucleic acid encoding a polypeptide having 99% identify to SEQ ID NO:4. Each of these methods, alone or in combination, is effective for isolating and cloning

desired gene-specific products, and all had been used successfully by skilled workers to clone genes prior to applicants' filing date. While some experimentation is required to carry out the methods of the invention, this experimentation is not undue, because it requires no more than routine methods. Thus, the enablement rejection should be withdrawn.

Rejection under 35 U.S.C. § 102(b)

The Examiner rejects claims 11-13, 15, 19, 20, 21, 24, and 25 as being anticipated by Neering et al. (Gene Bank Accession No. AF153912, hereafter "Neering") and Amano et al. (J. Virology 76:1109, 1995, and Gene Bank Accession Nos: D26580 and AB015885, hereafter "Amano"). Claims 11 and 16-18 are further rejected as anticipated by Lee (13th International Symposium of Poxvirus-Iridovirus, Sept. 2-6, 2000 and Gene Bank Accession No. AJ293568, hereafter "Lee"); and Claims 11-13, 15, and 16-18 are rejected as anticipated by Paulose et al. (Microbial Pathogenesis 25: 33-41, 1998, hereafter "Paulose"). Applicants note that claims 19 and 20 have been cancelled.

Claims 11-13, 15, 21, 24, and 25, which feature Yatapox nucleic acids, now require SEQ ID NO:5, which the Examiner has indicated is free of prior art, or SEQ ID NO:4. Neering, Amano, Lee, and Paulose fail to disclose SEQ ID NOs: 4 or 5. Thus, the anticipation rejection by these references should be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 11-13, 15, 19-22, 24-26, 32, 33, and 47 were rejected as obvious over Neering, in view of Panicali (U.S. Pat. No. 5,656,465). Applicants note that claims 19 and 20 have been cancelled. Claims 11, 22, 24,and 32, and their dependent claims, have been amended to specify SEQ ID NO:5.

To establish a *prima facie* case of obviousness under §103, the Examiner must demonstrate that the differences between the claimed invention and the prior art are such that the subject matter as a whole would have been obvious, at the time the invention was made, to a person having ordinary skill in the art. *See* 35 U.S.C.§103(a) (Supp. III 1997); *In re Dembiczak*, 175 F.3d 994, 998, 50 USPQ2d 1614, 1616 (Fed. Cir. 1999). Where "claimed subject matter has been rejected as obvious in view of a combination of references, a proper analysis under §103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should . . . carry out the claimed process; and (2) whether the prior art would have revealed that in so . . . carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Neering, as noted above, does not describe SEQ ID NO:5. Neering also does not provide motivation to obtain the nucleic acid sequence of SEQ ID NO:5. Neering merely teaches the nucleic acid sequence of a 2108 base pair fragment of the Tanapox viral

genome.

Panicali does not make up for the deficiencies of Neering in supporting this rejection. Panicali teaches a viral vector useful for transforming a cell. Neither Panicali nor Neering teaches or suggests obtaining the nucleic acid sequence of SEQ ID NO:5. Thus, the rejection of the claims over Neering in view of Panicali should also be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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